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Commentary

Aromatase Inhibitor and Potential Effect on Adult Height in Growth Hormone Treated Adolescents with Prader-Willi Syndrome: A Commentary

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Classical genetic conditions with short stature as a major finding in adulthood include Noonan, Turner and Prader-Willi syndromes [1,2]. Noonan and Prader-Willi syndromes affect both males and females while Turner syndrome affects females only. These disorders have been recognized for several decades with published literature describing their features, genetic defects and natural histories but with lack of optimal treatment strategies [1,2]. They are accompanied by a list of comorbidities involving the cardiovascular system, stature, endocrinopathies, puberty and infertility. Endocrine dysfunctions affect the patient's well-being from birth through adulthood with limited information available for providers to transition from pediatric to adult healthcare and treatment options for subnormal growth to achieve adult stature.

Prader-Willi syndrome (PWS) occurs in about 1 in 20,000 livebirths and is caused most often by a paternal 15q11-q13 deletion followed by maternal disomy 15 where both chromosome 15s are from the mother [3]. A cardinal feature of PWS is infantile hypotonia which is accompanied by a poor suck, feeding problems and decreased energy levels with low body weight during the initial failure to thrive clinical stage [4,5]. The length is typically normal in the first few months of life but falls below normal within the first year related to failure to thrive when nutrition is the main growth promoting factor and low growth with other hormone deficiencies. Short stature is particularly apparent during puberty with the median height falling below the 5th percentile when compared to unaffected individuals [6]. The average adult height of males with PWS without growth hormone treatment is 157cm and 145cm in females [6-8]. Early and continued medical care with surveillance is needed to achieve optimal adult height in this rare genetic disorder [2,4,5,7-11].

Individuals with PWS also present with several distinctive facial features including a narrow forehead, elongated skull, almond-shaped eyes, small nose and chin, decreased saliva, a dry mouth, caries and other dental issues [4]. Facial features are altered in PWS when receiving growth hormone which was approved for treatment in 2000 [5] with an elongated prominent high chin [12]. The use of larger growth hormone dose than recommended and poor supervision could lead to acromegaloid features. Feeding difficulties noted in infancy give way to excessive eating and hyperphagia in early childhood during the second stage of clinical course development which leads to morbid obesity, if not externally controlled. They present cognitive impairments including developmental delay in language and motor skills and are prone to aberrant behavior, temper tantrums, stubbornness, compulsions, self-injury and decreased pain threshold [4,5,7,8].

Our commentary focuses on the need for related medical care by the pediatric healthcare team prior to transitioning to adult services and assessing approaches to improve stature that positively impact adult height in genetic syndromes where short stature is a cardinal feature, such as Prader-Willi syndrome. In addition, hormone deficiencies are common in this rare genetic disorder requiring treatment early affecting body composition, strength, metabolism, growth and stature. Growth hormone is often prescribed in infancy in PWS once the diagnosis is genetically confirmed as growth hormone deficiency is reported in the majority of patients with PWS. Short stature is seen in 90% of cases and feeding problems with a poor suck are cardinal features [2,4,7,8].

Our commentary was stimulated by the natural history of PWS specifically the endocrinopathies, pubertal issues, short stature and hormone replacement needs with new reports of aromatase inhibitors and growth hormone treatment that may improve predicted adult height in non-syndromic pubertal boys with idiopathic short stature [13-16] with application to PWS. We also point out that related medical care required by the pediatric healthcare team is needed prior to transitioning to adult services for improvement of stature impacting adult height in genetic syndromes where short stature is a cardinal feature. As noted, hormone deficiencies are common in PWS affecting not only body composition and obesity but also strength, metabolism, growth and stature. Growth hormone is often prescribed in infancy in PWS once the diagnosis is genetically confirmed and patients are cleared for treatment [2,5,10].

Sex Hormones, Puberty, Short Stature and Treatment

Hypothalamic dysfunction, hormone imbalances and decreased physical activity and metabolic rate along with increased caloric intake can cause life threatening obesity recognized as a cardinal finding in PWS. Those with PWS are also prone to hypothyroidism, and other hormone deficiencies, puberty delay, and body composition disturbances with associated problems such as type II diabetes,

cardiovascular disease and infarctions with venous thromboembolism leading to increased mortality. The reported average age at death is 30 years [17] but with early diagnosis and appropriate medical care, life expectancy improve. The presence of obesity in those with PWS are associated with increased rates of metabolic syndrome, hypothalamic insufficiency and hypogonadism leading to low estrogen and testosterone levels. These should be monitored and treated accordingly. Primary and central hypogonadism with pubertal delay is observed in nearly all individuals with PWS and commonly associated with infertility. Hypogenitalism is typically present with cryptorchidism in PWS males [4,5,8,10].

Estrogen is an essential regulator of bone maturation, growth plate fusion, and cessation of longitudinal growth in both males and females. Decreased estrogen effects due to insensitivity or deficiency [18-21] are associated with slow epiphysis closure and exceptional long period of growth. Based on these observations, it can be postulated that longitudinal growth can be modulated by blocking estrogen biosynthesis with aromatase inhibitors (AI), which inhibit aromatization of C19 androgens [(T)] to C18 estrogens including for PWS, as well.

The off-label use of third-generation AI, such as letrozole and anastrozole, has been explored to increase adult height (AH) in boys with non-syndromic short stature. Studies in those pubertal boys have shown inconsistent results on the impact of AI on increased adult height but some investigations have shown beneficial effects [14,22-25]. However, Mauras et al. [15,16] did demonstrate a rise in predicted near adult height and AH in adolescent boys treated with a combination of growth hormone (GH) and AI for GH deficiency or idiopathic short stature (ISS) compared to those treated with GH only. Similarly, more recent studies by Yackobovitch–Gavan et al. [26] demonstrated that aromatase inhibitor treatment alone or with GH increases final height in short-statured pubertal boys with early onset puberty and ISS indicating a potential use in syndromic short stature disorders; hence, the selection of PWS for study. As noted, hypogonadism and hypogenitalism are characteristics of PWS along with premature adrenarche and excessive adipose tissue which is much higher than in the general population. We have also demonstrated acceleration of linear height velocity and long-term benefit with near adult height (AH) from growth hormone treatment (GHT) [10]. The adiposity seen in PWS with premature adrenarche may also accelerate growth velocity and a decrease in adult height.

The goal of a potential long-term study is warranted to compare the effect on AH after GH treatment alone and in combination with AI in males with PWS. A longitudinal study is needed in a cohort of PWS male children or adolescents readily available with genetically confirmed PWS to further characterize the impact of GHT alone and stoppage after achieving complete skeletal maturation and followup. GH and anastrozole group (GH-AI) analysis would be recorded and studied at chronological ages of 11 to 13 years, before attaining AH and for a period of time such as 5 years. The AH will be determined as the height attained when bone age is 16 years or when growth velocity for the preceding year had reached a plateau. Initial and final height-standard deviation score (HT-SDS) will be reported and analyzed in both groups with bone maturation assessed based on roentgenograms of the left hand and wrist. Furthermore, clinical manifestations of premature adrenarche or elevated plasma DHEA-S levels will be assessed and confirmed. Final adult height will be recorded in those receiving growth hormone alone (GHA) or in those with growth hormone and aromatase inhibitor (GH-AI) treatment to determine if an increased adult height would be found and recorded in those PWS males receiving both growth hormone and aromatase inhibitors to maximize their adult height prior to skeletal maturation. Side effects would be monitored and recorded such as pain, mood changes, nausea, vomiting, abdominal pain, or back pain.

Hence, our commentary and proposed study in a classical genetic disorder where short stature is a cardinal feature could be undertaken and treatment accessed using GH and AI treatment approaches in individuals with PWS at a young age. This would be prior to achieving adult height at a point where growth and stature could be positively influenced by treatment using pediatric health care approaches. This combined treatment approach and timing if successful to maximize adult stature may have a direct application for other genetic short stature disorders.

Keywords: *Genetic conditions, Prader-Willi syndrome, Clinical and genetic findings, Short stature, Treatment*

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